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ABSTRACT

Objectives: To determine whether current influenza vaccination is associated with reduced risk of major vascular events in patients with recent ischemic stroke or TIA of mainly atherothrombotic origin.

Methods: Data were pooled from 2 prospective cohort studies, the OPTIC Registry (n = 3,635) and the AMISTAD Study (n = 618), and from the randomized PERFORM Trial (n = 19,120), all of which included patients with recent ischemic stroke or TIA. Influenza vaccination status was determined in 23,110 patients. The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or vascular death up to 2 years. Secondary outcomes were myocardial infarction and stroke separately.

Results: Influenza vaccination had no association with the primary outcome in the propensity score–matched cohort (hazard ratio 0.97, 95% confidence interval [CI] 0.85–1.11; $p = 0.67$) or in the propensity score–adjusted cohort (hazard ratio 1.00, 95% CI 0.89–1.12; $p = 0.99$). Similarly, the risk of stroke and myocardial infarction did not differ between the vaccinated group and the unvaccinated group; in the matched cohort, the hazard ratio was 1.01 (95% CI 0.88–1.17; $p = 0.89$) for stroke and 0.84 (95% CI 0.59–1.18; $p = 0.30$) for myocardial infarction.

Conclusions: Influenza vaccination was not associated with reduced outcome events in patients with recent atherothrombotic ischemic stroke after considering all baseline characteristics (including concomitant medications) associated with influenza vaccination. *Neurology*® 2014;82:1905–1913

GLOSSARY

AMISTAD = Asymptomatic Myocardial Ischemia in STroke and Atherosclerotic Disease; **CI** = confidence interval; **OPTIC** = Outcomes in Patients with TIA and Cerebrovascular disease; **PERFORM** = Prevention of cerebrovascular and cardiovascular Events of ischemic origin with teRutroban in patients with a history oF ischemic strOke or tRansient ischeMic attack.

There is increasing evidence that influenza infection could be a trigger for stroke and other major vascular events. Various observational studies have reported a close temporal association between influenza and the occurrence of stroke, suggesting a potential causal link.[1–5] However, whether immunizing patients against influenza reduces the risk of major vascular events remains uncertain. Two case-control studies, one involving 90 patients and the other 370 patients with a recent stroke, showed that influenza vaccination in the previous year was associated with a 50% reduction in the odds of stroke,[6,7] whereas another case-control study found no association.[8] Two large cohort studies in populations older than 65 years suggested a reduced rate of stroke in those vaccinated against influenza.[9,10] To date, no randomized trial has tested the effect of influenza vaccination on major vascular event recurrence in stroke patients, and conflicting results have been found in patients with coronary artery disease.[11–14] A healthy user bias may explain the beneficial effect observed in these observational studies because it was recently shown in a large observational study using data from a large multinational study that influenza vaccination was associated with a far greater benefit effect on vascular events than expected,

Supplemental data at Neurology.org

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PERFORM, OPTIC, and AMISTAD coinvestigators are listed on the *Neurology*® Web site at Neurology.org.

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suggesting bias.[15] Propensity score matching may help to estimate the effect of an intervention such as influenza vaccination by accounting for covariates that predict receiving the treatment, matching attempts to mimic randomization by creating a treated sample comparable to the untreated sample.[16]

In the present study, we aimed to evaluate whether influenza vaccination was associated with lower risk of major cardiovascular events in patients with recent ischemic stroke or TIA enrolled in 2 cohort studies and one randomized trial, using propensity score–adjustment approaches to minimize confounding bias.

METHODS

Data sources. Data from 3 prospective studies of patients with a recent ischemic stroke or TIA were combined to determine the impact of vaccination against influenza on recurrent cardiovascular events: the single-center Asymptomatic Myocardial Ischemia in STroke and Atherosclerotic Disease (AMISTAD) Study, designed to assess the prevalence and impact of systemic atherosclerosis on the risk of major vascular events[17]; the international multicenter Outcomes in Patients with TIA and Cerebrovascular disease (OPTIC) Registry, designed to evaluate determinants of 2-year recurrence risk in patients with noncardioembolic ischemic stroke[18]; and the international, multicenter, randomized Prevention of cerebrovascular and cardiovascular Events of ischemic origin with teRutroban in patients with a history oF ischemic strOke or tRansient ischeMic attack (PERFORM) Trial, designed to assess the superiority of terutroban, a specific TP receptor antagonist, compared with aspirin in the prevention of cardiovascular ischemic events in patients with recent noncardioembolic ischemic stroke or TIA.[19]

Study patients. Eligible patients in the AMISTAD Study were men or women aged 18 years or older who had a nondisabling (Rankin Scale score <5) cerebral infarction documented by imaging, or a TIA, in the previous 10 days.[17] A total of 618 patients were recruited between June 2005 and December 2008. Follow-up visits were performed at 3 and 6 months, and at 1-year intervals thereafter; the minimum follow-up duration was 4 years. The current analysis is based on the database lock in December 2010, when the last patient completed 2-year follow-up.

The OPTIC Registry enrolled patients aged 45 years or older with a recent noncardioembolic TIA or minor stroke (<6 months), in low- and middle-income countries. A total of 3,635 participants were recruited from 245 sites in 17 countries between January 2007 and December 2008. Follow-up visits were performed every 6 ± 1 months during the 2-year follow-up period.[18]

The PERFORM Trial enrolled patients with a recent noncardioembolic cerebral ischemic event, such as ischemic stroke within the previous 3 months, or TIA within the previous 8 days. A total of 19,120 participants were recruited from 802 sites in 46 countries between February 2006 and April 2008. Follow-up visits were performed at 1, 3, and 6 months, and every 6 months thereafter; the minimum follow-up duration was 2 years.[19]

Standard protocol approvals, registrations, and patient consents. All participants in the 3 studies provided written informed consent before enrollment.

Data collection and definitions. Data on baseline characteristics, medical history, and medications were collected from individual patients at enrollment using a standardized form specific to each study. Influenza vaccination status was determined by use of a self-reported questionnaire at the enrollment visit in each study. In the PERFORM Trial, influenza vaccination status was also recorded at each follow-up visit. The primary study outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or vascular death up to 2 years. Secondary outcomes were myocardial infarction and stroke separately (either fatal or nonfatal events). Events were adjudicated in the AMISTAD Study and the PERFORM Trial by blinded evaluation using medical records but were not adjudicated in the OPTIC Registry.

Statistical analysis. Continuous variables are reported as means ± SDs. Categorical variables are reported as frequencies and percentages. Patients were divided into 2 groups on the basis of influenza vaccination at enrollment. Baseline characteristics, risk factors, and medications were compared between the 2 groups (for both combined data and for data from the individual studies) using the Student *t* test for continuous variables and the χ^2 test for categorical variables. In view of the significant differences in key baseline characteristics (table 1), we used propensity score matching to assemble a cohort in which all of the measured baseline characteristics would be well-balanced across groups.[20] In each study separately, we estimated a propensity score using a nonparsimonious multivariable logistic regression model, with influenza vaccination use as the dependent variable and all of the characteristics listed in table 1 as covariates.[21] We therefore matched the selected vaccinated patients with unvaccinated patients who had a similar propensity score by using the greedy matching protocol (i.e., a 1:1 matching algorithm without replacement) with a caliper width of 0.1.[20,22] Once the matched pairs were established, we pooled the 3 matched cohorts for the main analysis. We estimated absolute standardized differences for all covariates before and after matching to evaluate the bias reduction using the propensity score matching method. An absolute standardized difference of less than 10% for a given covariate indicates an inconsequential imbalance.[23] Comparisons in baseline characteristics between the matched groups were done using the paired Student *t* test and the Cochran-Mantel-Haenszel χ^2 test for qualitative variables.

In the primary analysis, we performed survival analyses on the matched cohort. Cumulative event curves were constructed using the Kaplan-Meier method, and the event rates were determined from 2-year Kaplan-Meier estimates. Events that occurred after the 2-year follow-up were not included in the analysis. We compared the risk of cardiovascular outcomes between the vaccinated and unvaccinated groups using a Cox proportional hazard regression model stratified on the matched pairs. A first sensitivity analysis was done in the overall cohort using a Cox proportional hazard regression model with the propensity score and study as covariates.[21] The proportional hazards assumption was verified by using Schoenfeld residuals.

Because influenza vaccination status was recorded at each follow-up visit in the PERFORM Trial, we also assessed the impact of influenza vaccination in a time-varying Cox regression analysis. This secondary sensitivity analysis, restricted to the PERFORM Trial, attempted to account for changes in influenza vaccination status over time by including a time-dependent covariate into the propensity score–adjusted Cox model. In addition, in the matched pooled cohort, we replicated the survival analyses in each study separately, and performed key subgroup analyses based on age (≤75 vs >75 years), sex, qualifying event for inclusion (stroke vs TIA), and history of coronary artery disease. Heterogeneity across studies and subgroups was quantified by

Table 1 Patient characteristics according to vaccination status, before and after propensity score matching

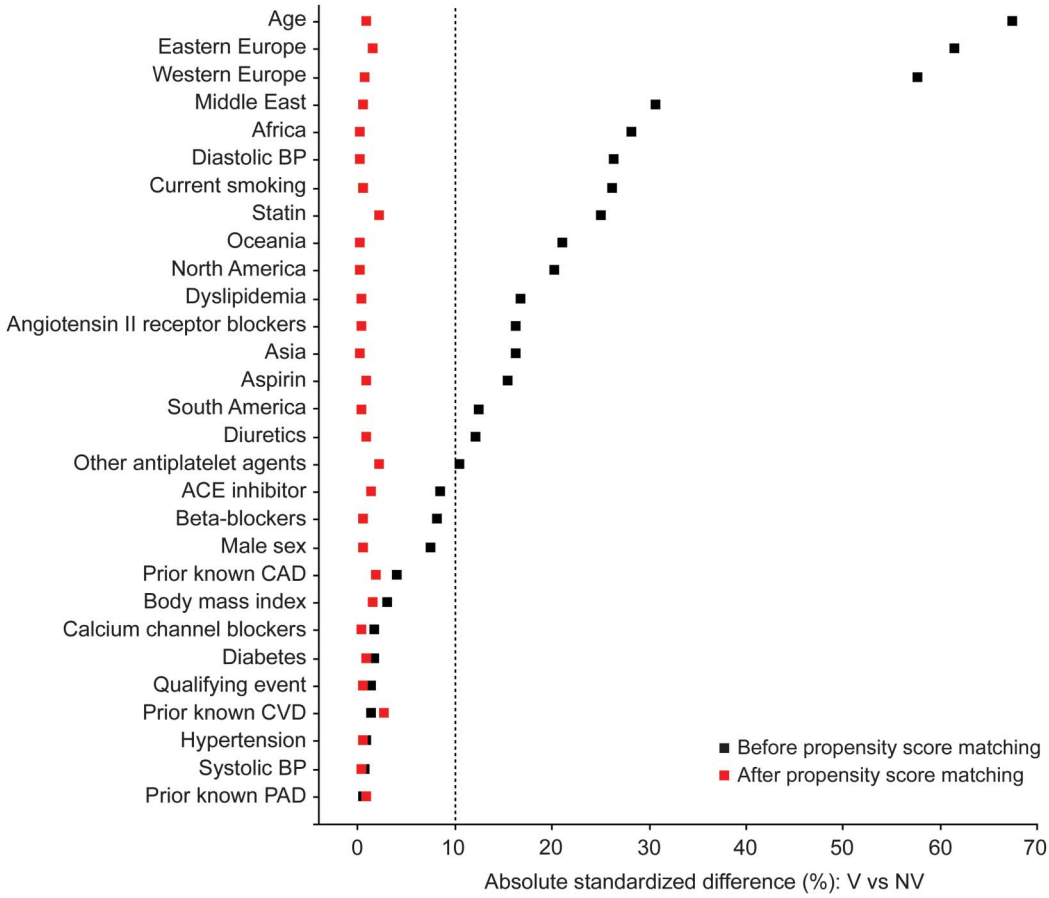
	Before propensity score matching			After propensity score matching		
Factor	NV (n = 17,363)	V (n = 5,747)	p	NV (n = 5,054)	V (n = 5,054)	p
Age, y, mean (SD)	65.5 (8.4)	70.9 (7.8)	<0.001	69.9 (7.9)	70.0 (7.5)	0.55
Men	10,902 (62.8)	3,399 (59.1)	<0.001	3,034 (60.0)	3,049 (60.3)	0.76
Body mass index, kg/m^2, mean (SD)	27.1 (4.4)	27.0 (4.3)	0.043	27.1 (4.4)	27.0 (4.2)	0.41
Systolic blood pressure, mm Hg, mean (SD)	138 (18)	138 (17)	0.62	138 (17)	138 (17)	0.82
Diastolic blood pressure, mm Hg, mean (SD)	81 (10)	78 (9)	<0.001	79 (10)	79 (9)	0.91
Qualifying event						
Stroke	15,082 (86.9)	5,019 (87.3)	0.36	4,445 (88.0)	4,436 (87.8)	0.78
TIA	2,281 (13.1)	728 (12.7)		609 (12.0)	618 (12.2)	
Region						
Western Europe	4,946 (28.5)	3,210 (55.9)	<0.001	2,785 (55.1)	2,803 (55.5)	0.92
Eastern Europe	5,583 (32.2)	488 (8.5)		510 (10.1)	487 (9.6)	
North America	214 (1.2)	268 (4.7)		185 (3.7)	187 (3.7)	
South America	2,267 (13.1)	1,009 (17.6)		905 (17.9)	913 (18.1)	
Asia	1,828 (10.5)	348 (6.1)		351 (6.9)	347 (6.9)	
Oceania	266 (1.5)	309 (5.4)		206 (4.1)	209 (4.1)	
Africa	1,272 (7.3)	89 (1.6)		88 (1.7)	86 (1.7)	
Middle East	987 (5.7)	26 (0.5)		24 (0.5)	22 (0.4)	
Medical history						
Hypertension	14,479 (83.4)	4,773 (83.1)	0.55	4,192 (82.9)	4,179 (82.7)	0.73
Diabetes mellitus	4,971 (28.6)	1,692 (29.4)	0.24	1,512 (29.9)	1,492 (29.5)	0.66
Dyslipidemia	7,640 (44.1)	3,018 (52.6)	<0.001	2,610 (51.6)	2,600 (51.4)	0.84
Current smoking	4,960 (28.7)	1,019 (17.8)	<0.001	985 (19.5)	974 (19.3)	0.77
Known cardiovascular disease	3,666 (21.2)	1,250 (21.8)	0.37	1,017 (20.1)	1,075 (21.3)	0.15
Known coronary artery disease	3,551 (20.5)	1,086 (18.9)	0.009	873 (17.3)	911 (18.0)	0.31
Known peripheral artery disease	782 (4.5)	267 (4.7)	0.71	231 (4.6)	221 (4.4)	0.63
Medications						
Aspirin	9,189 (52.9)	3,480 (60.6)	<0.001	3,050 (60.4)	3,025 (59.9)	0.60
Other antiplatelet agent	9,582 (55.2)	2,871 (50.0)	<0.001	2,426 (48.0)	2,482 (49.1)	0.26
Oral anticoagulant	1,304 (7.5)	614 (10.7)	<0.001	523 (10.4)	532 (10.5)	0.77
Angiotensin-converting enzyme inhibitor	8,802 (50.7)	2,668 (46.4)	<0.001	2,383 (47.2)	2,349 (46.5)	0.49
Calcium channel blocker	4,428 (25.5)	1,512 (26.3)	0.23	1,292 (25.6)	1,302 (25.8)	0.82
Diuretic	5,149 (29.7)	2,033 (35.4)	<0.001	1,711 (33.9)	1,734 (34.3)	0.62
β-Blocker	4,040 (23.3)	1,541 (26.8)	<0.001	1,284 (25.4)	1,299 (25.7)	0.73
Angiotensin II receptor blocker	2,220 (12.8)	1,076 (18.7)	<0.001	904 (17.9)	911 (18.0)	0.86
Statin	10,279 (59.2)	4,085 (71.1)	<0.001	3,570 (70.6)	3,517 (69.6)	0.24

Abbreviations: NV = patients not vaccinated against influenza; V = patients vaccinated against influenza.
Data are n (%) of patients unless otherwise indicated.

formal interaction tests. Given the statistically nonsignificant results, we performed a post hoc power analysis using the observed 2-year event rate (10%). With 80% power, we could detect a hazard ratio of 0.84 with 5,054 matched pairs and a hazard ratio of 0.87 with the overall cohort (n = 23,110). Statistical testing was conducted at the 2-tailed α level of 0.05, except for tests for homogeneity, in which an α level of 0.10 was chosen. Data were analyzed using the SAS software version 9.3 (SAS Institute, Cary, NC).

RESULTS Among 23,353 patients enrolled in the PERFORM Trial, the OPTIC Registry, and the AMISTAD Study, 23,110 with available information on influenza vaccination at baseline and with at least one postbaseline follow-up assessment were included in the present analysis (figure e-1 on the *Neurology*® Web site at Neurology.org). Overall, 5,747 patients

Figure 1 Absolute standardized differences in baseline characteristics between vaccinated and unvaccinated patients before and after propensity score matching



ACE = angiotensin-converting enzyme; BP = blood pressure; CAD = coronary artery disease; CVD = cerebrovascular disease; NV = not vaccinated against influenza; PAD = peripheral artery disease; V = vaccinated against influenza.

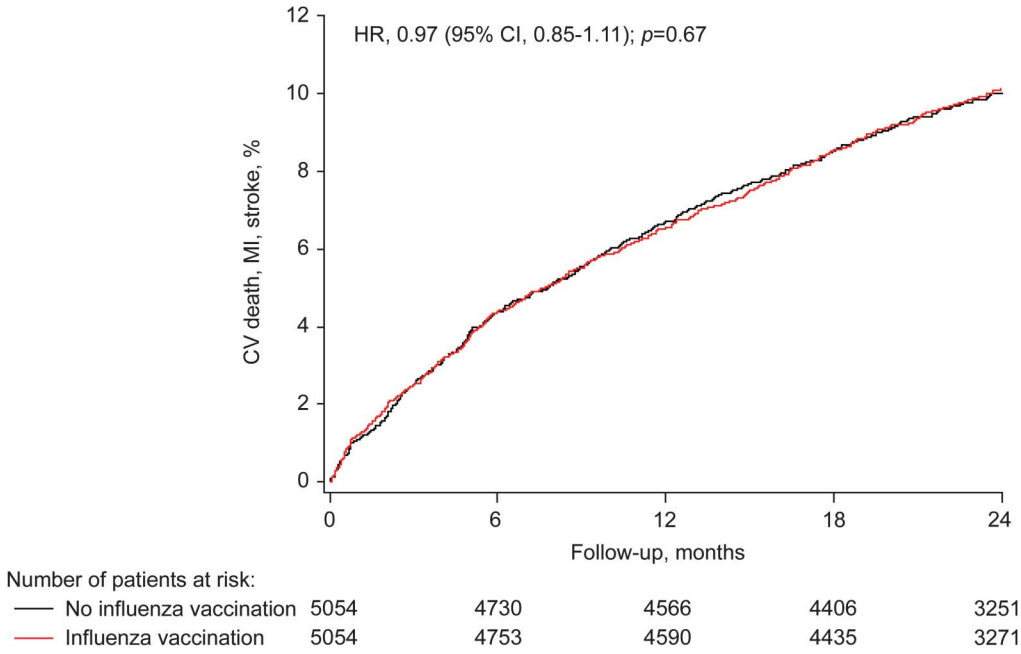
(25%) were vaccinated against influenza at baseline: 5,174 from the PERFORM Trial (27%), 416 from the OPTIC Registry (12%), and 157 from the AMISTAD Study (27%).

As shown in table 1, there were significant differences in baseline characteristics between vaccinated and unvaccinated patients. Compared with unvaccinated patients, vaccinated patients were on average older, with a slightly higher percentage of women, were more likely to be recruited in western Europe, to be dyslipidemic, to have a lower diastolic blood pressure, and to be taking aspirin, oral anticoagulants, diuretics, β-blockers, angiotensin II receptors, and statins. They were less likely to be current smokers, to have a history of coronary artery disease, and to be taking angiotensin-converting enzyme inhibitors. The propensity score matched 5,054 vaccinated patients (88% of vaccinated patients) with 5,054 unvaccinated patients. There were no significant differences in baseline characteristics between the 2 groups after matching; all absolute standardized differences were lower than 10%, suggesting an adequate match (figure 1). The baseline characteristics for each study before and after propensity score matching are shown in tables e-1 to e-3; overall, there were no relevant differences after propensity score matching in any of the studies (figures e-2 to e-4).

In the overall matched cohort, 988 patients experienced at least one primary event (vascular death, myocardial infarction, or stroke) during the 2 years of follow-up (Kaplan-Meier estimate, 10%). As shown in figure 2, the rate for combined primary events in vaccinated patients was similar to the rate in patients who were not vaccinated (hazard ratio 0.97, 95% confidence interval [CI] 0.85–1.11; $p = 0.67$). Similar results were found in the propensity score–adjusted model including the entire study cohort (table 2). There was no significant difference in the risk of secondary outcomes: the matched hazard ratio associated with vaccination was 0.84 (95% CI 0.59–1.18; $p = 0.30$) for myocardial infarction and 1.01 (95% CI 0.88–1.17; $p = 0.89$) for stroke.

Although there was no significant heterogeneity across studies ($p = 0.22$), there was a nonsignificant

Figure 2 Cumulative incidence curve of cardiac death, myocardial infarction, and stroke by influenza vaccination use in propensity score–matched sample



CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction.

decreased risk of combined primary events in vaccinated patients in comparison to unvaccinated patients in the OPTIC Registry (figure e-5) (hazard ratio 0.71, 95% CI 0.47–1.05; $p = 0.09$). A similar result was observed for both myocardial infarction (hazard ratio 0.53, 95% CI 0.23–1.26; $p = 0.15$) and stroke outcomes (hazard ratio 0.67, 95% CI 0.41–1.10; $p = 0.11$) (table e-4). In the other 2 studies, no such differences were observed (figures e-6 and e-7).

In vaccinated patients enrolled in the PERFORM Trial, the proportion of patients who remained vaccinated during the study follow-up was 71% at 1 year and 72% at 2 years. Of the unvaccinated patients at enrollment, 12% were vaccinated at 1 year and 17% at 2 years. In time-varying analysis adjusted for propensity score, influenza vaccination was not associated with the combined outcome (hazard ratio 1.05, 95% CI 0.93–1.18; $p = 0.42$) or with myocardial infarction alone (hazard ratio 1.02, 95% CI 0.75–1.37) or stroke alone (hazard ratio 1.08, 95% CI 0.95–1.22).

The risks of the primary and secondary outcomes in the propensity score–matched sample were similar across subgroups of vaccinated and unvaccinated patients (figure 3).

Table 2 Risk of cardiovascular events in patients with and without influenza vaccination

	Propensity score-matched analysis				Propensity score-adjusted analysis[a]			
	No. of events (Kaplan-Meier estimates)				No. of events (Kaplan-Meier estimates)			
Outcome	NV (n = 5,054)	V (n = 5,054)	Hazard ratio (95% CI)[b]	p	NV (n = 16,901)	V (n = 5,672)	Hazard ratio (95% CI)[c]	p
Nonfatal MI, nonfatal stroke, vascular death	491 (10.0)	497 (10.1)	0.97 (0.85-1.11)	0.67	1,620 (9.9)	568 (10.3)	1.00 (0.89-1.12)	0.99
MI, fatal/nonfatal	78 (1.6)	64 (1.3)	0.84 (0.59-1.18)	0.30	253 (1.6)	83 (1.5)	0.82 (0.62-1.08)	0.15
Stroke, fatal/nonfatal	400 (8.2)	417 (8.5)	1.01 (0.88-1.17)	0.89	1,314 (8.1)	470 (8.5)	1.03 (0.91-1.16)	0.66

Abbreviations: CI = confidence interval; MI = myocardial infarction; NV = patients not vaccinated against influenza; V = patients vaccinated against influenza.

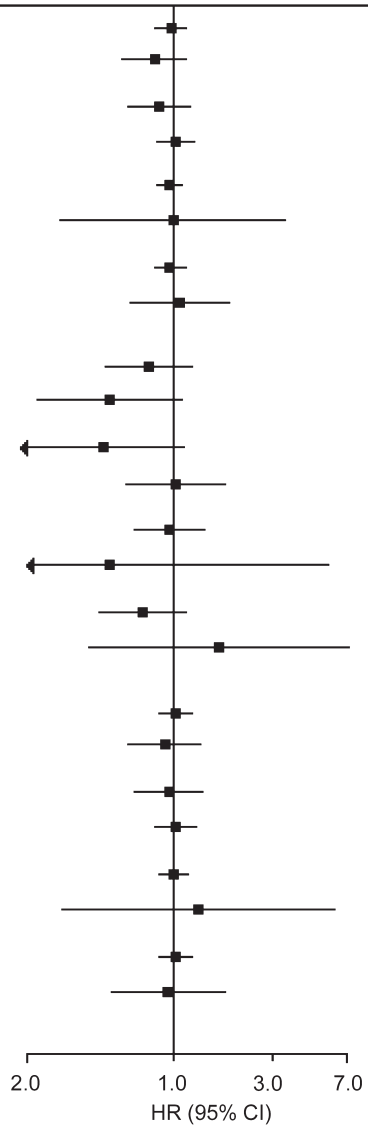
[a] After excluding 537 patients with missing propensity score (2.7% of unvaccinated patients and 1.3% of vaccinated patients).

[b] Cox-regression model stratified on the matched pairs.

[c] Cox-regression model stratified on study and adjusted on propensity score (introduced as continuous variable).

Figure 3 Risk of cardiovascular events with use of influenza vaccination in propensity score–matched sample by key subgroup

Outcome	Subgroup	CIV(-)	CIV(+)	HR(95%CI)	*P* for interaction
Cardiac death, MI, stroke	Age ≤75 yrs	336 / 3774	358 / 3837	0.98 (0.83-1.16)	0.55
	Age >75 yrs	155 / 1280	139 / 1217	0.82 (0.58-1.16)	
	Women	173 / 2020	181 / 2005	0.87 (0.62-1.21)	0.36
	Men	318 / 3034	316 / 3049	1.04 (0.85-1.28)	
	Stroke*	449 / 4445	448 / 4436	0.97 (0.84-1.12)	0.79
	TIA*	42 / 609	49 / 618	1.00 (0.29-3.45)	
	No CAD history	356 / 4181	360 / 4143	0.98 (0.83-1.15)	0.98
	CAD history	135 / 873	137 / 911	1.08 (0.63-1.86)	
MI (fatal/nonfatal)	Age ≤75 yrs	53 / 3774	46 / 3837	0.77 (0.48-1.24)	0.65
	Age >75 yrs	25 / 1280	18 / 1217	0.50 (0.22-1.11)	
	Women	30 / 2020	18 / 2005	0.47 (0.19-1.15)	0.14
	Men	48 / 3034	46 / 3049	1.04 (0.61-1.78)	
	Stroke*	67 / 4445	59 / 4436	0.96 (0.66-1.41)	0.13
	TIA*	11 / 609	5 / 618	0.50 (0.04-5.51)	
	No CAD history	50 / 4181	39 / 4143	0.73 (0.45-1.17)	0.23
	CAD history	28 / 873	25 / 911	1.67 (0.40-6.97)	
Stroke (fatal/nonfatal)	Age ≤75 yrs	279 / 3774	303 / 3837	1.04 (0.86-1.25)	0.64
	Age >75 yrs	121 / 1280	114 / 1217	0.92 (0.62-1.37)	
	Women	130 / 2020	155 / 2005	0.96 (0.66-1.41)	0.76
	Men	270 / 3034	262 / 3049	1.04 (0.83-1.30)	
	Stroke*	367 / 4445	378 / 4436	1.01 (0.86-1.18)	0.76
	TIA*	33 / 609	39 / 618	1.33 (0.30-5.96)	
	No CAD history	298 / 4181	309 / 4143	1.04 (0.87-1.24)	0.53
	CAD history	102 / 873	108 / 911	0.95 (0.51-1.78)	



*Qualifying event. Values are number of events/number of patients, unless otherwise indicated. Propensity score–matched HRs for use of influenza vaccination at baseline are reported with 95% CIs. CAD = coronary artery disease; CI = confidence interval; CIV = current influenza vaccination; HR = hazard ratio; MI = myocardial infarction.

DISCUSSION In this large, prospective, international study, we found that after considering all baseline characteristics associated with influenza vaccination, current immunization against influenza was not associated with a reduced risk of major adverse vascular events in patients with a recent ischemic stroke or TIA. This result contradicts previous positive cross-sectional studies.

Indeed, most epidemiologic studies published so far reported an association between influenza vaccination and stroke risk.[6,7,9,10] However, ours is not the first negative study. A recent case-control study found no association between stroke and influenza vaccination,[8] and negative results have also been found in the prevention of myocardial infarction.[24–26] There is also the possibility that, because of publication bias, other negative studies have not been published. However, above all, observational studies may be biased and this is particularly true for influenza vaccination studies. It has been suggested that a healthy user bias (also called healthy vaccine bias) attributed to differences between vaccinated and unvaccinated people may account for some or all previously observed risk differences.[27,28] Receipt of influenza vaccination is voluntary (even if recommended in fragile people) and thus may be preferentially used by healthier individuals, as illustrated by several inconsistencies. Observational studies have reported that influenza vaccination is

associated with a decrease in mortality of 50% or more during the influenza season, whereas influenza accounted for a maximum of 10% of all deaths, a risk reduction that far exceeds the expected plausible protective effect.[27] Moreover, a similar effect size has been observed, while influenza vaccination did not match the virus strain,[29] and was even greater outside the influenza season,[30] suggesting the presence of confounding because vaccine effectiveness is expected to occur only during the epidemic season. Finally, beneficial effects, similar in magnitude to those observed in the present study, were observed for diseases not reasonably attributable to influenza infection, such as hospitalization for trauma and injury.[30] To limit this bias inherent to the observational design of our study, we used propensity score matching, a sophisticated confounder modeling technique, and found no association between influenza vaccination and risk of a major vascular event. This result offers further evidence against the existence of a true positive effect of vaccination in the prevention of vascular risk.

This study was based on a large sample size, and we prospectively collected a considerable volume of data, allowing us to use the propensity score matching technique. Results were confirmed in a sensitivity analysis in the whole cohort, adjusted on the propensity score and in key subgroups of patients. Our population is quite homogeneous because only patients with a recent ischemic stroke or TIA were included and most of these events were related to atherosclerosis. Patients were prospectively followed up during 2 years.

Our study does, however, also have limitations. The present findings are derived from observational analyses, which are subject to well-known limitations. The first is the potential for confounding by measured or unmeasured variables, which cannot be ruled out, even after propensity score adjustment methods. In the present study, we had no information on lifestyle or socioeconomic status, data that could have influenced the vaccination status.[28] For example, one recent study using a large clinical database from 2 randomized trials (the ONTARGET and TRANSCEND trials), which enrolled 31,546 patients with a history of vascular disease (approximately 20% had a previous stroke or TIA) or diabetes mellitus with end-organ damage, assessed the association between influenza vaccination and the risk of a major vascular event using a propensity score, but with different covariates, including markers of healthy living.[15] This study found that influenza was associated with a strong decrease in major vascular events (31%–48%). However, the authors concluded that despite all efforts to limit bias, undetected bias probably explained their results, because a similar benefit association was found outside the epidemic period and a greater effect was observed for noncardiovascular death (ranging from 73% to 79%), which is not supposed to be influenced by influenza vaccination.[15] We were unable to confirm vaccination history with medical records, and some patients may have been misclassified, although self-report of vaccination history has a high sensitivity and specificity.[31] More importantly, we cannot exclude an immortality time bias, despite propensity score–matched analysis.[32]

In addition, most patients enrolled had noncardioembolic stroke, because cardioembolic stroke was an exclusion criterion in both the PERFORM Trial and the OPTIC Registry. We cannot exclude that influenza vaccination may have a beneficial effect in this particular subtype of ischemic stroke. The majority of our population was taking antithrombotic therapies, antihypertensive therapies, and lipid-lowering drugs, and because of regular follow-up visits in specialized centers, it is probable that vascular risk factors were strictly controlled, leaving little room for any additional benefit from influenza vaccination. Finally, we did not have information about the matching between circulating virus strains and the antigen in the vaccine in the different countries studied, and we did not evaluate the effect of vaccination in relation to the corresponding period of expected influenza activity and inactivity. These are important limitations because the protective effect of vaccination is believed to be related to influenza infection prevention.

Data on influenza vaccination and vascular risk have accumulated, including in stroke. The discrepancy between published results is probably inherent to bias, common in observational studies, but particularly difficult to apprehend in the context of influenza vaccination. A large randomized placebo-controlled trial would be needed to definitively address whether influenza vaccination reduces the risk of major vascular events in stroke patients, although it is unlikely that such a trial will be funded. However, the conflicting results found in studies in patients with coronary heart disease show that many factors come into play and that the choice of study population is particularly important. For example, the effect of vaccination appears greater in patients with unstable rather than stable coronary artery disease.[11–14] Regarding cerebral infarction, the problem of etiologic subtypes is added to the list of factors to be considered. In our study, with a majority of patients with cerebral infarction of atherothrombotic origin, vaccination was not associated with a reduced risk.

In a large cohort of patients with recent ischemic stroke or TIA matched for variables associated with influenza vaccination, influenza vaccination was not associated with a reduction in the risk of major vascular events.

AUTHOR CONTRIBUTIONS

P.A. participated in the conception and design of the study. P.C.L., J.L., and P.A. analyzed and interpreted the data. PERFORM, AMISTAD, and OPTIC Registry investigators provided study material or recommended

patients. J.L. performed statistical analysis. P.C.L. and J.L. wrote the manuscript. All authors reviewed and approved the manuscript.

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